REMARKS

A. Disposition of Claims

Claims 1-51 are pending in this application. Claims 25-51 were withdrawn from consideration. Claims 3, 6, 9, 12, 15, 18, 21, and 24 are canceled herewith without prejudice. Claims 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, and 22-23 are amended herewith to conform to issued US Patent No. 6,458,541 to Sklar et al., which the image file wrapper indicates was a first office action allowance, and thus for reasons unrelated to patentability. Support for the amendment is located throughout the specification, for example, at paragraph [0008]. No new matter has been added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

B. Compliance with 35 USC 112/1 enablement

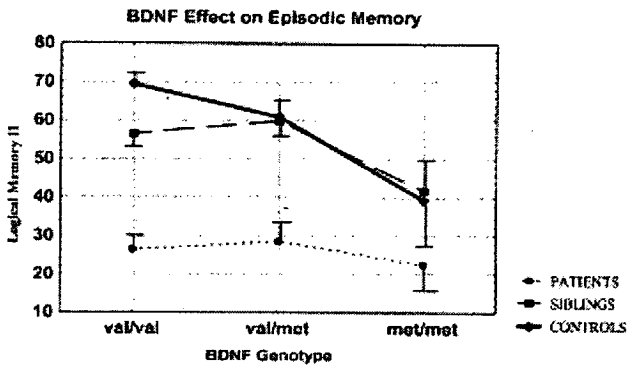
The Patent Office rejected Claims 1-24 under 35 USC 112/1 as failing to meet the enablement requirement. Under MPEP 2164, the test for enablement is whether one skilled in the art could make or use the subject matter defined by the claims without undue experimentation. Under MPEP 2164.01(a), the Wands factors are to be considered in determining whether any necessary experimentation is undue. The claims have been amended. Here, the specification is enabling with respect to the claimed subject matter.

i) First, there is considerable direction and guidance in the specification. Verbal Memory: Referring to the specification at paragraph [0008], and the post-filing date art Egan et al., Cell 112:257 (Jan 2003), of record, which published the invention, and the post-filing date art Bath and Lee, Cogn. Affect. Behav. Neurosci. 6: 79 (2006), of record, which showed recognition by others: The inventors examined the effects of a valine (val) to methionine (met) substitution in the 5′ pro-region of the human brain-derived neurotrophic factor (BDNF) protein. In human subjects, the met allele was associated with impaired hippocampal dependent verbal memory,

assayed with memory scores, hippocampal activation, assayed with functional magnetic resonance imaging (fMRI), and hippocampal n-acetyl aspartate (NAA), assayed with magnetic resonance imaging (MRI) spectroscopy. While they found no relationship between BDNF genotype and schizophrenia, their results demonstrate that BDNF and its val/met polymorphism plays a role in hippocampal function and hippocampal dependent verbal memory in humans.

In a first experiment, the inventors examined the effects of BDNF genotype on measures of hippocampal dependent verbal memory in a cohort of subjects, including normal controls, patients with schizophrenia, and their unaffected siblings, using measures from a test of hippocampal dependent verbal memory. Patients with schizophrenia had substantially lower scores compared to controls, while siblings were intermediate between these groups. Referring to the specification at paragraph [0008] and Egan et al. 2003 at Fig. 1A, in the entire sample, BDNF genotype had a significant effect on these memory scores. Referring to Egan et al. 2003 at Fig. 1A, in the group of controls alone, BDNF genotype also had a significant effect on memory scores. Referring to Egan et al. 2003 at Fig. 1A, while including patient and sibling groups did not substantially add to the results, both groups showed the same effect seen in controls with met/met subjects tending to score lower than other genotype groups. Referring to Egan et al. 2003, post hoc comparisons in the normal subjects alone showed that met/met homozygotes had lower scores compared to val/val and val/met, while in the entire cohort, met/met homozygotes had lower scores compared to the other two genotype groups. Referring to Egan et al. 2003 at Fig. 1B, within each group (controls, siblings, patients), each genotype group was well matched on a variety of demographic parameters, indicating they did not account for the effect of BDNF genotype. Fig. 1 of Egan et al. 2003 is reproduced below for the convenience of the Patent Office:

A



B

	Patients			Siblings			Controls		
Genotype Group (number of subjects)	Val/val (138)	Val/met (56)	Met/met (9)	Val/val (206)	Val/met (85)	Met/met (14)	Val/val (91)	Val/met (36)	Met/met (6)
Age	36.8 (9.2)	35.7 (8.6)	32.5 (10.2)	37.2 (8.8)	35.8 (8.9)	34.7 (8.8)	35.0 (9.7)	34.1 (8.9)	39.3 (8.4)
Gender (M/F)	109/29	45/11	7/2	91/115	31/54	7/7	43/48[a]	26/10[a]	4/2
Education years	13.8 (2.2)	13.9 (2.6)	13.9 (2.8)	15.8[a] (2.5)	15.1[a] (2.4)	15.3 (2.6)	16.2 (2.4)	16.7 (3.2)	17.7 (4.3)
Reading Comprehension	101.3 (12.3)	100.9 (12.7)	105.1 (10.0)	106.5 (11.2)	104.7 (11.8)	104.5 (11.2)	106.3 (10.2)	106.2 (10.2)	104.7 (12.6)
IQ	92.9 (12.6)	91.1 (13.1)	92.3 (13.5)	106.2 (13.1)	106.1 (13.1)	104.7 (13.1)	107.6 (10.7)	109.1 (10.2)	105.7 (12.6)
Semantic Memory	33.5 (11.8)	33.9 (11.5)	33.2 (14.1)	42.1 (11.1)	39.2 (11.3)	41.7 (10.5)	44.11 (9.2)	48.0 (9.8)	44.3 (10.5)
Working Memory	37.0 (12.0)	37.4 (12.8)	42.0 (14.9)	44.0 (9.5)	44.7 (10.6)	43.4 (7.3)	47.3 (9.5)	46.1 (10.3)	40.1 (8.1)

Figure 1. Effect of BDNF val66met Genotype on Episodic Memory(A) BDNF val66met genotype and episodic memory scores (± SE) from the WMS-R (delayed recall) in three samples studied.(B) Demographic and cognitive data by genotype. Means (± SD) are presented. Genotype groups are well matched.

Referring to Egan et al. 2003, similar effects of BDNF genotype were seen with another test of hippocampal dependent verbal memory. Post hoc comparisons again showed that met/met homozygotes had lower scores compared to val/val and val/met groups. Continuing with Egan et al. 2003, no effect of BDNF genotype was seen on other types of memory, such as prefrontal component dependent memory, semantic memory, and working memory/executive function. These results indicate that the val66met polymorphism exerts a robust effect on hippocampal dependent verbal memory.

Egan et al. 2003 viewed the effects of BDNF and COMT as mediated through "modular" cognitive elements. Although they conducted an extensive cognitive test battery, the inventors did not detect an effect of BDNF on IQ or any other cognitive ability. A recent study of the role of the COMT gene on working memory and prefrontal physiology, but not IQ, provides further evidence for the view of mediation through "modular" cognitive elements of the effects of COMT and BDNF. Egan et al., Proc. Natl. Acad. Sci. USA 98: 6917 (2001), of record.

Hippocampal Function: Referring to the specification at paragraph [0008], and the post-filing date art Egan et al. 2003, which published the invention, and the post-filing date art Bath and Lee 2006, which showed recognition by others: In a second experiment, the inventors investigated the effect of BDNF val66met genotype on in vivo hippocampal functional magnetic resonance imaging (fMRI) response. BDNF val/met subjects showed abnormal hippocampal activation during memory tasks and were significantly different compared to val/val subjects. Referring to Egan et al. 2003, the inventors examined the BDNF val66met genotype effect on hippocampal fMRI response in a second independent cohort. The BDNF val/met subjects again showed abnormal hippocampal activation and were significantly different compared to val/val subjects. Referring to Egan et al. 2003, demographic and cognitive data for both cohorts indicated that genotype groups were well matched and covariance analyses revealed no effects of any differences on hippocampal activation patterns.

ii) Second, there was a high level of skill in the art at the time the application was filed. The level of skill in the molecular biology art was that of a postdoctoral fellow working in the laboratory. *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 57 USPQ2d 1449, 1518 (D. Mass. 2001). Thus, the level of skill in the art was high.

iii) Third, all of the methods needed to practice the invention were well known. At the time of the 31 August 2001 priority date, for guidance regarding such conditions, refer to, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York; and Ausubel et al., 1989, Current Protocols in Molecular Biology, Green Publishing Associates, Inc., and Wiley & Sons, Inc., New York. Verbal Memory: Neuropsychological tests were known in the art, e.g., Egan et al., Biol. Psychiatry 50: 98 (Nov 2001), of record, and Weickert et al., Arch. Gen. Psychiatry 57: 907 (2000), attached. Hippocampal Function: Functional magnetic resonance imaging was known in the art, e.g., Callicott et al., Cereb. Cortex 10: 1078 (Nov 2000), of record, and Ogawa et al., Proc. Natl. Acad. Sci. USA 89: 5951 (1992), of record. Antibodies that specifically recognize the BDNF valine66 but not the BDNF methionine66 variant: Refer to, for example, Harlow and Lane, 1988, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York, describing how an antibody may be raised against a unique peptide sequence by synthesizing the peptide, conjugating it for immunization, immunizing rabbits, purifying the antibodies against the immunizing peptide, and examining the specificity of antibodies by western blot, all as shown by Zhou et al., J. Neurochem. 91: 704 (2004), attached, in which an antibody is produced that specifically recognizes the precursor BDNF, but not mature BDNF, by western blot.

iv) Per MPEP 2164.01(a), the In re Wands Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." Similarly, here, as indicated above, there was considerable direction and guidance in the specification; there was a high level of skill in the art at the time the application was filed; and all of the methods needed to practice the invention were well known. Thus, here, considering all the factors related to the enablement issue, it must be concluded that the specification is enabling with respect to the claims at issue.

C. Compliance with 35 U.S.C. § 112/2

The issue is whether Claims 1-12 are in compliance with 35 U.S.C. § 112/2 as being definite. The rule is that the claims must particularly point out and distinctly claim the subject

matter that applicant regards as the invention. Claims 1-12 were rejected as being indefinite for recitation of the phrase "correlated with" because it encompasses both positive and negative limitations. In contrast, Claims 13-24 use the phrase "indicative of". It was suggested that Claims 1-12 be amended to recite the phrase "indicative of" rather than "correlated with". Amendment was made. Because the claims have been amended to delete the phrase "correlated with" and substitute "indicative of", the conclusion is that Claims 1-12 are in compliance with 35 U.S.C. § 112/2 as being definite.

D. Compliance with 35 USC 102(e)

The issue is whether Claims 1-12 are in compliance with 35 USC 102(e) or anticipated by US Patent 6,458,541 to Sklar et al. The rule according to MPEP 2131 is that to anticipate a claim, the reference must teach every element of the claim. US Patent 6,458,541 to Sklar et al. describes the val allele as deleterious and indicative of bipolar disorder in individuals. Here, the claims require that the met allele is deleterious and indicative of not schizophrenia but impaired hippocampal function and hippocampus dependent verbal memory in humans. The conclusion is that the reference fails to anticipate the claims, thus the claims are in compliance with 35 USC 102(e).

E. Compliance with 35 USC 103(a)

The issue is whether Claim 1 and claims dependent thereon are in compliance with 35 USC §103(a) or unpatentable over Hariri et al., Program No. 620.12 Abstract Viewer/Itinerary Planner, Washington, DC, Society for Neuroscience, 2002, 8/19/2002 in view of US Patent 6,458,541 to Sklar et al. The Patent Office takes the position that, with regard to hippocampal function, the present application is not entitled to the benefit of priority of U.S. Provisional Patent Appl. No. 60/316,736 filed 31 Aug 2001, but is properly entitled to the benefit of priority of International Patent Appl. No. PCT/US02/28086 filed 30 Aug 2002. Without agreeing that there is no antecedent basis in U.S. Provisional Patent Appl. No. 60/316,736 filed 31 Aug 2001, Applicant agrees that there is exact antecedent basis in International Patent Appl. No. PCT/US02/28086 filed 30 Aug 2002. Consequently, Hariri et al. 8/19/2002 qualifies in terms of date as 35 USC 102(a)/103 intervening art. The rule according to MPEP 715.01(c) is that, unless it is a statutory bar (which it is not), a rejection based on a publication may be overcome by a showing that it is a publication of applicant's own work. Attached is In Re Katz Declaration

indicating that Applicant (i.e., Weinberger et al.) is the sole inventive entity, and the co-authors who were not additionally named as co-inventors were involved only with assay and testing sufficient to be listed as co-authors but are not considered co-inventors. Accordingly, the showing removes Hariri et al., Program No. 620.12 Abstract Viewer/Itinerary Planner, Washington, DC, Society for Neuroscience, 2002, 8/19/2002 as a reference under 35 USC 102(a)/103. As for US Patent 6,458,541 to Sklar et al., as described above, it does not teach or suggest all the elements of the claims. The conclusion is the claims are in compliance with 35 U.S.C. §103(a).

CONCLUSION

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 12/22/06

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